Quantitative polymorphism of complement receptor type 1 (CR1) in patients undergoing haemodialysis

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Abstract

Background. The level of complement receptor type 1 (CR1) on erythrocytes (E-CR1) is determined by the presence of high (H) or low (L) expression alleles. We investigated whether acquired loss of E-CR1 occurs in haemodialysis patients and, if so, which factors may contribute to acquired loss of E-CR1 in these patients.

Methods. The E-CR1 level was determined in 195 Japanese haemodialysis patients, and we selected patients with a high or low E-CR1 level. In patients with low E-CR1 expression, sequence analysis of polymorphic sites (A3650G and C5507G) in the CR1 gene was performed. To assess the effect of the type of dialysis membrane used in the patients with low E-CR1 expression, the dialysis membrane was changed from a cellulose membrane to a biocompatible membrane (to a polyacrylonitrile membrane and then to a polysulfone membrane). To evaluate the susceptibility of E-CR1 to proteolysis, erythrocytes were incubated with various concentrations of trypsin, and the level of remaining CR1 on the erythrocytes was determined.

Results. Among patients with high E-CR1 expression (n = 30), 87% had HH alleles and 13% had HL alleles. Among patients with low E-CR1 expression (n = 29), 24% had LL alleles, 45% had HL alleles and 31% had HH alleles. Nucleotides 3650G and 5507G in the CR1 gene were associated with the L allele. Nucleotides 3650A and 5507C were associated with the H allele. Only one patient with HH alleles had nucleotides 3650G and 5507G. Three months after changing the haemodialysis membrane, the E-CR1 level significantly increased (P < 0.02). The proteolysis curves of E-CR1 of patients with low or high E-CR1 expression and normal controls were similar.

Conclusion. Use of a non-biocompatible dialysis membrane may contribute to acquired loss of E-CR1 in haemodialysis patients.

Keywords: complement receptor type 1; CR1; dialysis membrane; haemodialysis; polymorphism

Introduction

Complement receptor type 1 (CR1) is a transmembrane glycoprotein and is a member of the regulators of the complement activation family [1]. CR1 is expressed on several cell types including erythrocytes, B cells, polymorphonuclear leukocytes, monocytes, follicular dendritic cells and glomerular podocytes [2,3]. CR1 is a receptor for C3b and C4b, and recently was also found to be a receptor for C1q and mannan-binding lectin (MBL) [4,5]. The major role of CR1 on erythrocytes (E-CR1) is to mediate the binding of C3b-opsonized immune complexes and to carry them to the spleen and liver where they are removed [6]. CR1 is also a cofactor in the factor I-mediated cleavage of C3b and C4b, and CR1 has decay-accelerating activity towards both the classical and alternative pathways of C3 and C5 convertases [7].

Although the level of E-CR1 expression is regulated by two CR1 alleles that determine high (H allele) or low (L allele) CR1 expression and that differ in having genomic HindIII fragments of different lengths [8], acquired low levels of E-CR1 have been seen among patients with systemic lupus erythematosus (SLE), acquired immunodeficiency syndrome (AIDS) and rheumatoid arthritis (RA) with HH alleles [9-12]. These patients have abnormal clearance of immune complexes; however, the mechanism through which the E-CR1 level is reduced is not clear. Since nearly 90% of the CR1 in the circulation is found on erythrocytes, the amount of E-CR1 may be associated with host defence.

It is known that dialysis patients are in a state of acquired immunodeficiency [13]. Patients with end-stage renal disease are susceptible to infection and have defects of phagocytic function [13,14]. Therefore, we hypothesized that in patients undergoing...
haemodialysis, dysfunction of the host defence against infections is associated with a low level of E-CR1. However, we do not yet know whether acquired E-CR1 diminution occurs in dialysis patients. The purpose of this study was to investigate the relationship between the level of CR1 expression on erythrocytes and genetic polymorphism.

Materials and methods

**Screening for haemodialysis patients with low/high E-CR1 expression**

The E-CR1 level was determined in 195 Japanese patients undergoing haemodialysis at Kasukake-Kisen Hospital in Kasukake, Japan. All 195 patients were receiving recombinant erythropoietin therapy (epoetin α, range 4500–9000 IU/week) and there were no signs of haemolysis in any of the patients. The dialysis membrane used for haemodialysis was a cellulose membrane. Quantiﬁcation of E-CR1 was performed using Quantum Simply Cellular (QSC) (Flow Cytometry Standard Corp., Fishers, IN). QSC consists of uniform cell size microbeads with different calibrated capacities for binding to goat anti-mouse IgG on their surface. We determined the antibody-binding capacity (ABC) on erythrocytes using a calibration plot derived directly from a mixture of standards that were labelled with anti-CR1 (DAKO, Glostrup, Denmark). It was reasonable to use this method for comparison of the results of sequential experiments performed each day, and the coefficient of variation (CV) of anti-CR1 on the standard beads was <2%.

For staining of CR1 on erythrocytes obtained from the subjects, a 50 μl aliquot of blood was suspended in 1 ml of phosphate-buffered saline (PBS) containing 10 mM EDTA (EDTA–PBS), and this was centrifuged at 2000 r.p.m. at room temperature for 10 min to recover the erythrocytes. A 10 μl aliquot of anti-CR1 [T05 (DAKO), 150 μg/ml] was added to 1 x 10^6 erythrocytes and allowed to react at room temperature for 30 min. After the incubation, 1 ml of PBS was added and this was centrifuged at 2000 r.p.m. at room temperature for 5 min and the supernatant was removed. The samples were then allowed to react with 20 μl of rabbit anti-mouse immune globulin conjugated with phycoerythrin F(ab′)2 (50 μg/ml; DAKO) as the secondary antibody at room temperature for 30 min. The cells were washed with PBS, suspended in 500 μl of PBS, and analysed by flow cytometry. Negative IgG1 (100 μg/ml; DAKO) was used as a negative control. All samples were analysed three times and the CV was within 3.2%.

In our study, a high level of E-CR1 expression was deﬁned as an ABC on the surface of erythrocytes of >1200 (mean ± 1 SD), and a low level of E-CR1 expression was deﬁned as an ABC on the surface of erythrocytes of <621 (mean ± 1 SD). According to these criteria, the patients were screened for low or high E-CR1 expression. In patients with a low or high level of E-CR1 expression, laboratory examinations including complete blood cell count and blood chemistry were performed.

**Complement C3 and C5 levels**

The serum levels of complement C3 and C5 were determined by the single radial immunodiffusion method and were expressed relative to the respective level in normal human serum.

**HindIII restriction fragment length polymorphism (RFLP) of intron 27 of the CR1 gene**

In patients with a high (n = 30) or low level of E-CR1 expression (n = 29), genomic DNA was extracted using the GenTLE kit (Takara Shuzo Co., Ltd, Ohtsu, Japan). The HindIII RFLP in intron 27 of the CR1 gene was analysed as described previously [15]. The polymerase chain reaction (PCR) products of the HindIII fragments of intron 27 were categorized by length as follows: H allele, 1800 bp; L allele, 1300 bp and 500 bp.

**Sequence analysis of polymorphic sites in the CR1 gene**

Exons 22 (A3650G) and exon 33 (C5507G) of the CR1 gene were amplified and sequenced as described previously [16]. The following sequence primers were used: exon 22, forward primer, CTTTCACAGTGTCAGC; reverse primer, AGACGCAGCCCTCTCT; exon 33, forward primer, CGCACCCCACCCAGA, reverse primer, AACAGCA GGAAAGAAA. Nucleotide numbers were according to Klickstein et al. [17].

**Effect of the type of dialysis membrane used in haemodialysis on the E-CR1 level**

We assessed the effect of the type of dialysis membrane used in haemodialysis on the level of CR1 expression on erythrocytes. In patients with low E-CR1 expression and homozygous HindIII alleles (LL alleles, n = 7; HH alleles, n = 9) who were using a cellulose membrane (AMSD18M; Asahi Medical Co., Ltd, Tokyo, Japan), the dialysis membrane was changed to a biocompatible membrane; the dialysis membrane was first changed to a polycrylonitrile (PAN) membrane (PAN 17DX; Asahi Medical Co., Ltd, Tokyo, Japan) and then to a polysulphone (PS) membrane (APS 150; Asahi Medical Co., Ltd, Tokyo, Japan). The patients with HH alleles (n = 9) used a PAN membrane for 6 months and then a PS membrane for the following 6 months. The patients with LL alleles (n = 7) used a PAN membrane for 3 months and then a PS membrane for the following 9 months. Immediately before a new type of membrane was used, a blood sample was obtained and the E-CR1 level was determined as described above.

**Proteolysis of E-CR1**

In order to evaluate the susceptibility of E-CR1 to proteolysis, erythrocytes were subjected to proteolysis by various concentrations of trypsin (Sigma, St Louis, MO) as previously described [18]. The erythrocytes of the following subjects were used: patients who originally had low E-CR1 expression, that were obtained 1 year after changing the haemodialysis membrane to a biocompatible membrane (LL alleles, n = 2; HH alleles, n = 3); patients with high E-CR1 expression (HH alleles, n = 3); and normal subjects with high E-CR1 expression (HH alleles, n = 2) or low E-CR1 expression (LL alleles, n = 1). After digestion with trypsin, the level of the remaining E-CR1 was determined as described above. All samples were analysed in triplicate.
**CR1 polymorphism in haemodialysis patients**

**Activity of serum protease**

The level of serum protease activity before and after a haemodialysis session was measured using casein as the substrate. Serum samples were obtained before and after a haemodialysis session. A 1 ml aliquot of 1% casein in PBS was mixed with 1 ml of the patient’s serum and incubated at 35°C. After 20 min, 3 ml of 5% trichloroacetic acid was added and this was incubated for 1 h. The reaction mixture was centrifuged at 3000 r.p.m. at 20°C for 20 min and the absorbance was measured at 280 nm. We defined 1 U of serum protease activity as the level of serum protease activity that increased the absorbance by 0.1 per min.

**Statistical analysis**

All data are shown as mean±SD. The age, length of the haemodialysis period and laboratory findings of the patients with low or high E-CR1 expression were compared by the Mann–Whitney U-test. The percentage of patients with diabetic nephropathy was analysed by the χ² test. Comparison of the E-CR1 levels and laboratory findings before and after changing the membrane was performed by the Wilcoxon test.

**Results**

**Screening for haemodialysis patients with high or low E-CR1 expression**

The level of E-CR1 on the erythrocytes of 195 patients undergoing haemodialysis was measured (Figure 1). The patients with high E-CR1 expression [1506±126 (mean±SD) ABC; n = 30] and those with low E-CR1 expression (508±87 ABC; n = 29) were selected for further analysis. Their underlying diagnoses are shown in Table 1. There were no significant differences in age, length of the haemodialysis period or haematological parameters (erythrocyte count, haemoglobin, haematocrit, reticulocyte count) between the patients with low or high E-CR1 expression. However, the prevalence of diabetic nephropathy among the patients with low E-CR1 expression was significantly higher than that among the patients with high E-CR1 expression (38 vs 10%; P < 0.02). The characteristics of the selected patients are summarized in Table 1.

Among the patients with low E-CR1 expression (n = 29), no patient had low complement levels of C3 or C5 (C3, 84±16%; C5, 91±15%, both normal in all 29 patients).

**HindIII RFLP**

Among the 30 patients with high E-CR1 expression, 87% had homozygous alleles (HH, n = 26; CR1, 1503±132 ABC, mean±SD) and 13% had heterozygous alleles (HL, n = 4; CR1, 1525±80 ABC). Among the 29 patients with low E-CR1 expression, 24% had homozygous LL alleles (n = 7; CR1, 389±60 ABC), 45% had heterozygous HL alleles (n = 13; CR1, 554±57 ABC) and 31% had homozygous HH alleles (n = 9; CR1, 534±50 ABC).

**Sequence analysis of polymorphic sites in the CR1 gene**

The results of the sequence analysis of nucleotides 3650 and 5507 of the CR1 gene in the patients with low E-CR1 expression are summarized in Figure 2. Nucleotides 3650G (predicted amino acid, Arg1208) and 5507G (predicted amino acid, Arg1827) were tightly associated with the L allele. Nucleotides 3650A (His1208) and 5507C (Pro1827) were associated with the H allele. Only one patient with HH alleles had nucleotides 3650G (Arg1208) and 5507C (Pro1827).

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**Table 1. Characteristics of patients undergoing haemodialysis who had high or low E-CR1 expression**

<table>
<thead>
<tr>
<th></th>
<th>Patients with high E-CR1 expression (n = 30)</th>
<th>Patients with low E-CR1 expression (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-CR1 on (ABC)</td>
<td>1506±126</td>
<td>508±87</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63±12</td>
<td>59±14</td>
</tr>
<tr>
<td>Haemodialysis period (months)</td>
<td>94±78</td>
<td>86±70</td>
</tr>
<tr>
<td>Erythrocyte count (×10⁹/μl)</td>
<td>3.09±0.31</td>
<td>3.23±0.51</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>9.8±1.1</td>
<td>9.9±0.9</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>31.3±2.9</td>
<td>30.5±4.2</td>
</tr>
<tr>
<td>Reticulocyte count (%)</td>
<td>13±4</td>
<td>14±5</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>n = 26</td>
<td>n = 11</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>n = 3</td>
<td>n = 11</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>n = 1</td>
<td>n = 1</td>
</tr>
<tr>
<td>Nephrosclerosis</td>
<td>n = 3</td>
<td></td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>n = 2</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>n = 1</td>
<td></td>
</tr>
</tbody>
</table>

*We measured the level of CR1 on the erythrocytes of 195 Japanese patients undergoing haemodialysis. Patients with high or low E-CR1 expression were selected for this study.

bHigh E-CR1 expression was defined as an ABC of >1280.

cLow E-CR1 expression was defined as an ABC of <621.

dAntibody-binding capacity.

Fig. 1. Distribution of the level of CR1 on erythrocytes obtained from 195 patients undergoing haemodialysis. E-CR1 levels are indicated as antibody-binding capacity (ABC).
Effect of changing the dialysis membrane to a biocompatible membrane on the E-CR1 level and proteolysis of E-CR1

In 16 patients with low E-CR1 expression and homozygous HindIII alleles, the effect of changing the dialysis membrane to a PAN membrane and then to a PS membrane on the level of E-CR1 expression was studied (Figure 3). Three months after changing the membrane from a cellulose membrane to a PAN membrane, the level of E-CR1 expression among the 16 patients had significantly increased ($P < 0.02$), and it had increased remarkably in three patients with HH alleles to an ABC of 751, 834 and 993 (patients HH-1, HH-2 and HH-3 respectively). Two patients with HH alleles died during the study; one patient died 1 month after the membrane was changed to a PS membrane and the second patient died 3 months after it was changed to a PS membrane. After changing the membrane to a biocompatible membrane, the E-CR1 level increased by a smaller degree in the patients with LL alleles than in those with HH alleles (Figure 3A and B). At 1 year after changing the membrane to a biocompatible membrane, the E-CR1 level of the patients with HH alleles was maintained at an even higher level (patients with HH alleles: before changing membrane, CR1, 545 ± 36 ABC, mean ± SD; 6 months after changing the membrane, CR1, 666 ± 215 ABC; 1 year after changing the membrane, CR1, 729 ± 170 ABC; 1 year after changing the membrane vs before changing membrane; $P < 0.05$, $n = 7$), and the E-CR1 level of five of the seven patients with LL alleles increased in comparison with that before changing the membrane to a biocompatible membrane. The erythrocyte count, haemoglobin, haematocrit and reticulocyte count at 3 months after changing the membrane did not differ significantly from the respective level prior to changing the membrane among the HH patients and among the LL patients (Table 2).
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Table 2. Changes in the erythrocyte count, haemoglobin level, haematocrit and reticulocyte count before and after changing the haemodialysis membrane to a biocompatible membrane in patients with low E-CR1 expression

<table>
<thead>
<tr>
<th>CR1 genotype</th>
<th>Before changing membrane</th>
<th>3 months after changing to a PAN membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte count (x10⁶/µl)</td>
<td>LL (n = 7)</td>
<td>3.02 ± 0.46</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>LL (n = 7)</td>
<td>9.3 ± 0.8</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>LL (n = 9)</td>
<td>10.2 ± 0.7</td>
</tr>
<tr>
<td>Reticulocyte count (%)</td>
<td>LL (n = 7)</td>
<td>29.9 ± 3.0</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.

*The membrane was changed from a cellulose membrane to a biocompatible PAN membrane.

**Patients with LL alleles (n = 7).

***Patients with HH alleles (n = 9).

In order to evaluate the susceptibility of the E-CR1 of the three patients with HH alleles with a remarkable increase in E-CR1 (patients HH-1, HH-2 and HH-3) to proteolysis, the erythrocytes obtained 1 year after changing to a biocompatible membrane were incubated with various concentrations of trypsin. The erythrocytes of two patients with LL alleles, three patients with HH alleles who originally had high E-CR1 expression, one normal control with LL alleles, and two normal controls with HH alleles were also studied. Similar proteolytic cleavage curves were seen in the patients and normal control(s) with the same alleles. The E-CR1 molecules of the normal control and haemodialysis patients with LL alleles showed slightly higher resistance to proteolysis with trypsin than the E-CR1 molecules of the normal controls and haemodialysis patients with HH alleles (Figure 4).

Additionally, we measured the serum protease activity before and after a haemodialysis session in the low CR1 expression group (HH, n = 9; LL, n = 7). The change in serum protease activity among the patients was variable. There was no significant difference in the level of serum protease activity before and after haemodialysis. Among those who were switched from the cellulose membrane to the PAN membrane, the serum protease activity when they were using the cellulose membrane did not differ significantly from that when they were using the PAN membrane (before dialysis, using cellulose membrane, 28 ± 34 U x 10⁻³/ml; PAN membrane, 27 ± 37 U x 10⁻³/ml; after dialysis, using cellulose membrane, 11 ± 12 U x 10⁻³/ml; PAN membrane, 14 ± 20 U x 10⁻³/ml).

Discussion

In the present study, we found that a portion of the haemodialysis patients with low E-CR1 expression had HH alleles. This suggests that acquired loss of E-CR1 occurred in these patients. Xiang *et al.* [16] showed that in Caucasians, the sequence of the L allele had the following substitutions of amino acids in comparison with the sequence of the H allele: His1208 to arginine and Pro1827 to arginine. Due to these substitutions, the E-CR1 of individuals with LL alleles was susceptible to proteolysis by serum proteases. However, the L allele in African-Americans was not strongly associated with the quantity of E-CR1 [19]. Prior to starting this study, we expected that haemodialysis patients with HH alleles who had low E-CR1 expression would have amino acid substitutions in CR1. However, there were no amino acid substitutions at positions 1208 and 1827 in CR1 except in one patient. This patient with HH alleles had nucleotides 3650G (Arg1208) and 5507C (Pro1827). Our data suggest that the CR1 polymorphism in the Japanese is similar to that in Caucasians.

Generally, loss of CR1 from erythrocytes occurs by proteolytic cleavage during the circulation of erythrocytes [18]. Erythrocytes have a long life span (~120 days), and E-CR1 is susceptible to proteolysis. However, there was no difference in the level of CR1 expression on leukocytes between normal individuals.
who were homozygous for the H or L allele [8]. We confirmed that the level of CR1 expression on the leukocytes of our patients with LL alleles was normal (data not shown). One possible cause of acquired loss of CR1 is augmentation of serum protease activity. Acquired loss of E-CR1 has been reported in patients with inflammatory diseases such as SLE, AIDS and RA [9–12], and the level of E-CR1 was correlated with disease activity [11,12]. It is suggested that E-CR1 undergoes proteolysis by serum proteases that are present in association with disease activity. Other evidence is that the level of CR1 on reticulocytes is normal in patients with SLE and AIDS [20]. In the present study, none of our patients had SLE, AIDS or other inflammatory disease as an underlying disease. The levels of complements C3 and C5 and the reticulocyte count were normal. It is not clear whether reduction of E-CR1 has already begun by the onset of end-stage renal disease. However, the E-CR1 level of patients with renal disease may gradually decrease according to disease activity.

Secondly, we considered the possibility that the dialysis membrane used in haemodialysis influences the level of E-CR1. The cellulose membrane used in haemodialysis is known to induce an inflammatory response. When blood comes into contact with the haemodialysis membrane, complement activation, release of proteases, leukotrienes and platelet-activating factor, several homeostatic reactions occur [21]. To assess the influence of the dialysis membrane, we changed the membrane from a cellulose membrane to a biocompatible membrane (PAN membrane and then a PS membrane) in patients with low E-CR1 expression who had homozygous alleles (HH and LL). The PS membrane and PAN membrane are known to be biocompatible membranes. After changing the dialysis membrane to a biocompatible membrane, the E-CR1 level increased in both the patients with HH and LL alleles. These results suggest that continuous use of a biocompatible membrane increases the level of E-CR1.

The E-CR1 after changing to a biocompatible membrane showed a similar resistance to trypsin as the E-CR1 of healthy controls and the E-CR1 of patients with high or low E-CR1 expression. It was reported that the allele (H, L) frequencies were similar between HIV-infected individuals and healthy controls [10]. Therefore, it was expected that there would be no difference in the distribution of H, L alleles between the HD patients and normal controls. Since the patients and normal control(s) with the same alleles had similar proteolytic cleavage curves, we believe that there were no differences in the E-CR1 molecules between the patients and normal controls with the same alleles. The E-CR1 molecules of the normal individual with LL alleles showed slightly higher resistance to proteolysis by trypsin than the E-CR1 of the HD patients and the normal controls with HH alleles. Individuals with L alleles have amino acid substitutions, H1208R and P1827R, in CR1. As Xiang et al. discussed in their report [16], a change to arginine would introduce a potential cleavage site for tryptic proteases. Therefore, the E-CR1 molecules of the normal individuals with LL alleles were susceptible to cleavage by proteases during the circulation of erythrocytes. Patients with SLE or AIDS show reduced E-CR1 expression, although they have a normal level of CR1 on their reticulocytes [20]. Further studies on proteolysis of CR1 on reticulocytes are warranted.

Although the response of the E-CR1 level upon changing the membrane to the PAN membrane and then to the PS membrane varied, it may have been reduced in both the patients with HH and LL alleles due to some influence of the non-biocompatible membrane. There is enhanced release of granulocyte proteinase during haemodialysis [22]. Additionally, we measured the serum protease activity before and after a haemodialysis session. However, the change in the level of serum protease activity before and after haemodialysis was variable among the patients and there was no significant change in activity. Further studies are needed to investigate which proteases are involved in the proteolysis of E-CR1. Another possibility is that a non-biocompatible membrane may increase vesiculation of E-CR1 molecules [23]. In our previous study, we found that in haemodialysis patients using a cellulose membrane, the E-CR1 levels before and after dialysis therapy did not differ significantly [24]. Therefore, loss of E-CR1 in haemodialysis patients probably occurs after using a non-biocompatible membrane in haemodialysis over a long period of time.

CR1 plays an important role not only in the regulation of complement activation, but also in the deposition of immune complexes. In view of host defence, low E-CR1 expression in patients undergoing haemodialysis may be a risk factor for infection. It was reported that recombinant erythropoietin therapy promotes E-CR1 expression [25]. In the present study, although the patients in the low E-CR1 expression group had received recombinant erythropoietin therapy, their E-CR1 level was low. Therefore, we consider that use of a biocompatible membrane in haemodialysis patients with HH alleles would prevent acquired loss of E-CR1.

In conclusion, acquired loss of E-CR1 was found among patients undergoing haemodialysis. It is suggested that acquired loss of E-CR1 occurs partly due to the influence of non-biocompatible dialysis membranes.

Conflict of interest statement. None declared.

References


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